



---

## **Guidance on the use of antiviral agents for the treatment and prophylaxis of Influenza, 2021/2022**

23/12/2021. V 3.1

---

---

## Table of Contents

What has changed since the last version? .....	4
Definitions.....	4
Introduction .....	6
Section 1: Treatment of persons with suspected or confirmed influenza .....	7
Section 1.1: Treatment of adults and children in the community/Emergency Departments with uncomplicated influenza .....	8
Section 1.2: Treatment of adults and children with complicated influenza .....	9
Section 1.3: Antiviral dosage and schedules for treatment.....	10
Section 1.3.1: Dosing in patients with renal dysfunction <sup>(5)</sup> .....	12
Section 1.3.2: Treatment of oseltamivir resistant influenza .....	13
Section 1.3.3: Management of influenza in critical care .....	13
Section 2: Post exposure prophylaxis .....	14
Section 2.1: Chemoprophylaxis in specific settings/ risk groups .....	15
Section 2.2: Selection of antivirals for post exposure chemoprophylaxis .....	17
Section 2.3: Antiviral dosage and schedules for post exposure chemoprophylaxis .....	18
Section 2.3.1: Dosing in patients with renal dysfunction <sup>(5)</sup> .....	18
Appendix A: Use of antivirals in pregnancy, breastfeeding, hepatic dysfunction .....	20
Appendix B: Antiviral medications authorised by the European Medicines Agency but not approved for use in the HSE .....	22
Appendix C: Frequently asked questions <sup>(5)</sup> .....	23
References.....	27

## Foreword

The influenza antiviral neuraminidase inhibitors (referred to herein as antivirals) are currently recommended for the treatment and prophylaxis (prevention) of seasonal influenza by a number of organisations worldwide including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) USA, the European Centre for Disease Prevention and Control (ECDC) and Public Health England (PHE).

This guidance summarises the current Irish recommendations for the use of antivirals in the treatment and prophylaxis of seasonal influenza. It draws on guidance already issued by PHE, ECDC, CDC and the WHO. It applies to the management of the currently circulating seasonal influenza viruses, influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B.

In keeping with the international guidance cited above, this guidance recommends the targeted use of antivirals for the treatment of uncomplicated influenza for specific at-risk groups in the population who are at increased risk of severe illness and death due to influenza. These groups include persons aged 65 years and older, pregnant women, residents of residential care facilities (RCF) for the elderly and others e.g. those with intellectual disabilities, those who are immunosuppressed and persons with chronic medical conditions. The guidance recommends antiviral treatment for patients with complicated influenza, regardless of whether or not they belong to an at-risk group. The targeted use of antivirals for post-exposure prophylaxis is recommended for those in at-risk groups.

Antivirals may be prescribed at any time in the secondary care setting for patients with suspected or confirmed influenza. However, it is recommended that prescribing of antivirals in primary care only occurs when the Health Protection Surveillance Centre (HPSC) issues an alert that influenza is circulating in the community<sup>1</sup>.

Due to the complex nature of influenza management, clinicians with enquiries about individual patients may wish to seek specialist advice about the use of antivirals from local consultant medical microbiologists, consultants in infectious diseases and virologists. Early specialist advice is recommended for the management of all patients with complicated influenza. Local Departments of Public Health should be notified of all local influenza/acute respiratory outbreaks. Separate guidance on management of influenza outbreaks in RCF is available on the [HPSC website](#).

As influenza management is a complex and evolving area, this guidance document may be updated during the season.

Clinicians may be aware of the Cochrane review on the efficacy of antivirals which was published in 2014. <sup>(1)</sup> In Ireland, recommendations for antiviral medications remain unchanged as per CDC (USA), the Infectious Disease Society of America (IDSA), ECDC and PHE. <sup>(2-6)</sup>

---

<sup>1</sup> Rates above the ILI threshold combined with sentinel GP influenza positivity >10% indicate the likelihood that influenza is circulating in the community.

## What has changed since the last version?

Version	Date	Changes from previous version	Draft by
3.1	20/12/2021	<ul style="list-style-type: none"> <li>Added in point in the introduction regarding the co-circulation of influenza and SARS-CoV-2</li> </ul>	HPSC
3.0	4/11/2021	<ul style="list-style-type: none"> <li>Description of zanamivir inhaled status expanded to “authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland”</li> <li>Removal of peramivir (withdrawn from use in the European Union 20/11/2020)</li> <li>Updated licensed indication for oseltamivir oral suspension to include treatment of those under 1 year, including full term neonates (as per EMA authorisation)</li> <li>Oseltamivir licensed for post exposure prevention of Influenza in those ≤ 1 year during a pandemic influenza outbreak</li> <li>SmPC links updated</li> <li>Change of wording in expression of dosing in all tables, for example BD changed to every 12 hours</li> <li>Rename and update of Appendix B and removal of all agents without an EMA authorisation for influenza treatment/prophylaxis</li> </ul>	AMRIC & HPSC
2.0	04/11/2020	<ul style="list-style-type: none"> <li>In the previous version it was stated that treatment with zanamivir (unlicensed available as inhaler) should be initiated within 36 hours of symptom onset. In this updated version this advice has been amended to state that treatment with zanamivir (unlicensed available as inhaler) should be initiated within 48 hours of symptom onset for adults and 36 hours for children.</li> <li>Previous recommendation that use of oseltamivir as treatment for longer than 5 days is an off-label use has been amended to state that use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.</li> </ul>	AMRIC & HPSC

## Definitions

**Uncomplicated influenza:** Influenza presenting with fever, cough, sore throat, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia), and sometimes gastrointestinal symptoms, but without any complications of influenza e.g. pneumonia, acute respiratory distress syndrome (ARDS).

**Complicated influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

### Risk factors for complicated influenza:

- a. Age 65 years and over
- b. Pregnancy (including up to two weeks post-partum)
- c. Children aged <2 years of age
- d. Chronic respiratory disease including those on medication for asthma
- e. Chronic heart, kidney, liver or neurological disease
- f. Diabetes mellitus
- g. Haemoglobinopathies
- h. Immunosuppression (whether due to treatment or disease e.g. HIV)
- i. Morbid obesity (BMI  $\geq 40$ )
- j. Those with any condition that can compromise respiratory function (e.g. cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder), especially those attending special schools/day centres.
- k. Those with Down Syndrome
- l. Persons with moderate to severe neurodevelopmental disorders such as cerebral palsy and intellectual disability
- m. Residents of nursing homes or RCF. <sup>(7, 8)</sup>

### Severe immunosuppression:

Examples of severe immunosuppression relevant to this guidance are outlined below. Degrees of immunosuppression are difficult to quantify and individual variation exists, therefore this list is not comprehensive.

#### A. Genetic diseases:

- Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
- Inborn errors in the interferon pathway

#### B. Cancer

- Receiving or within 6 weeks of receiving systemic cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies
- Receiving treatment or pending treatment for a haematological cancer
- Undergoing or within 6 weeks of surgery or radical radiotherapy for lung or head and neck cancer
- Advanced/ metastatic cancer
- Haematological - within 5 years of treatment

#### C. Transplantation:

- Listed for solid organ or haematopoietic stem cell transplant (HSCT)
- Post solid organ transplant at any time
- Post HSCT within 12 months

#### D. Patients with current graft-versus-host disease

#### E. Treatment

- Immunosuppressive treatments including but not limited to cyclophosphamide, rituximab, alemtuzumab, cladribine or ocrelizumab in the last 6 months
- High dose systemic steroids. The following doses of prednisolone (or equivalent dose of other glucocorticoid) are likely to be immunosuppressive:
  - Adults and children  $\geq 10$ kg:  $\geq 40$ mg/day for more than 1 week, or  $\geq 20$ mg/day for 2 weeks or longer
  - Children  $< 10$  kg: 2mg/kg/day for 2 weeks or longer
- HIV, not on treatment or CD4 count  $< 200 \times 10^6/L$  for adults

See Chapter 3a and Chapter 5a of the [National Immunisation Guidelines](#) for more details.

**This guidance should be used by clinicians in conjunction with the summary of product characteristics (SmPC) for these medicines, particularly with reference to the contraindications, interactions and adverse events.**

## Introduction

Influenza antiviral neuraminidase inhibitors (NAI) can be used to treat or prevent influenza. Antiviral medications are an important adjunct to vaccination and [infection prevention and control](#) practices in the control of influenza. Influenza vaccination and infection prevention and control practices are of the utmost importance in the prevention of influenza and are universally preferred over the administration of chemoprophylaxis. Separate guidance of the management of influenza in RCF is available on the [HPSC website](#)

SARS-CoV-2, causing COVID-19, is a major addition to the respiratory virus threats for the population <sup>(5)</sup>. The similar presentation of COVID-19 and Influenza makes the clinical diagnosis of influenza more challenging. This favours increased use of virological testing to guide case management and outbreak response. Non-pharmaceutical measures against COVID-19 also reduce the transmission of influenza <sup>(9)</sup>, however, influenza remains an important health risk when non-pharmaceutical interventions are not in place and in-person mixing occurs <sup>(10)</sup>. Coinfection of a patient with influenza and SARS-CoV-2 is possible and may be associated with increased mortality <sup>(11)</sup>. A review of the literature found no data to indicate any adverse impact of initiating neuraminidase inhibitors in patients with COVID-19. COVID-19 is not a contraindication to prescribing influenza antivirals where prompt initiation for suspected or confirmed influenza is required <sup>(6)</sup>.

Two antiviral medications are recommended for use in Ireland during the 2021-2022 influenza season: oseltamivir and zanamivir (inhaled & intravenous). It should be noted that zanamivir inhaler is authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland. Both oseltamivir and zanamivir are antiviral neuraminidase inhibitors which have activity against seasonal influenza A and B.

Early antiviral treatment can reduce the risk of complications from influenza, e.g. otitis media in young children, pneumonia and respiratory failure, shorten duration of illness among acutely ill patients and reduce morbidity, including hospitalisation, and mortality among patients with severe infection. <sup>(7, 12-13)</sup>

Antiviral treatment is recommended as early as possible for any patient with suspected or confirmed influenza who:

1. is hospitalised
2. has severe complications or progressive illness
3. is at higher risk from influenza complications (see risk groups for influenza in Definitions section, P. 4 & 5 of this document)

Antiviral treatment can also be considered for any previously healthy symptomatic outpatient (not at high risk) with suspected or confirmed influenza on the basis of clinical judgement. Ideally, treatment should be initiated early, within 48 hours of symptom onset if oseltamivir is being used and within 48 hours for adults or 36 hours for children if inhaled zanamivir is being used <sup>(7)</sup>

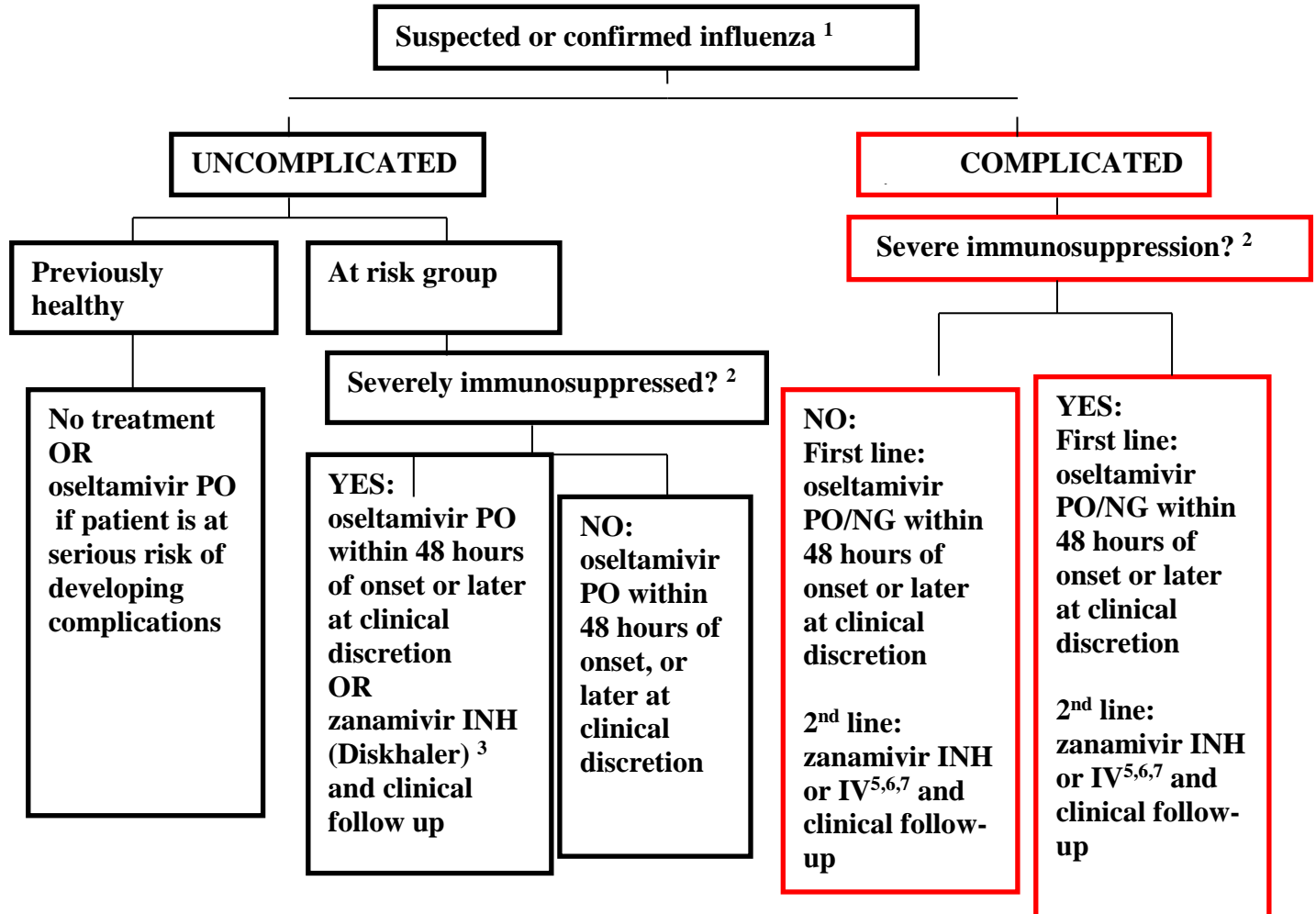
Clinical judgement on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since symptom onset is important when considering the initiation of antiviral therapy for high risk outpatients. The greatest benefit is achieved when antiviral therapy is commenced within 36 or 48 hours of symptom onset depending on which NAI is used. However, antiviral therapy may still be beneficial in patients with severe complicated or progressive illness and in hospitalised patients when administered more than 48 hours after symptom onset. <sup>(14, 15)</sup>

Empiric antiviral treatment is often necessary and providers should not delay commencement of treatment while awaiting confirmatory diagnostic test results or if specimens are not obtained. Patients with suspected influenza should complete a full course of antiviral treatment regardless of an initial 'influenza not detected' result, unless an alternative diagnosis can be established and clinical judgement suggests that influenza is an unlikely diagnosis. <sup>(7)</sup>

# Section 1: Treatment of persons with suspected or confirmed influenza

**Figure 1: Selection of antiviral therapy for the treatment of influenza**

Please refer to the definitions provided on Page 4 when using Figure 1.



- For treatment of suspected or confirmed oseltamivir resistant influenza, see section 1.3.2.
- Rapid emergence of oseltamivir resistance on treatment has been described in these patients (see Footnote 2). Resistance to oseltamivir has been described in infections from influenza A(H1N1)pdm09 subtype but not in those from influenza A(H3N2) to date (personal communication with NVRL). Clinicians may consider the use of zanamivir (inhaler authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland) as first line therapy in immunosuppressed patients with suspected or confirmed influenza A(H1N1)pdm09 based on clinical judgement. In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).
- Inhaled zanamivir may not be an effective delivery route in some patients, including those unable to administer the inhaler and patients with severe underlying respiratory disease. It is not licensed for use in children less than five years of age (see Footnote 3). The powder preparation for the inhaler should NEVER be made into nebuliser solution or administered to a mechanically ventilated patient.
- For treatment of complicated influenza, see section 1.2.
- Zanamivir is licensed for intravenous (IV) administration in Ireland and approved for reimbursement by the Health Services Executive for the following indication: - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of

<sup>2</sup> Footnote 1: Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among immunocompromised patients with influenza A(H1N1) pdm09. (16) Infection prevention and control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses.

<sup>3</sup> Footnote 2: Please note that this guidance describes the use of unlicensed medications for which there is limited safety and efficacy data. Specialist advice should always be obtained before using these products. This guidance represents the views of the HPSC influenza expert subgroup and not that of any manufacturer of medicines.



influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see [HPRA website](#)

6. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care). Where possible, patients who have good respiratory function despite their illness and who can use the inhaler should receive inhaled zanamivir rather than IV zanamivir unless there is multiorgan failure
7. Zanamivir is available for inhalation (authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland) or as an aqueous solution for IV use.

In general, influenza A(H1N1)pdm09 is considered to be higher risk for the development of oseltamivir resistance, while influenza A(H3N2) and influenza B are considered lower risk. There are many possible subtypes that cause human infection and further advice on the risk of individual subtypes can be obtained from a consultant medical microbiologist or virologist.

The risk of resistance is highest in people who are severely immunosuppressed. The selection of first line drugs in severely immunosuppressed individuals should take into account the subtype of influenza causing infection or, if not yet known, the dominant strain of influenza that is circulating during the influenza season. The dominant circulating strain of influenza can be obtained from the HPSC weekly influenza reports available on [HPSC website](#)

## **Section 1.1: Treatment of adults and children in the community/Emergency Departments with uncomplicated influenza**

**All patients should be advised of the symptoms of complicated influenza and told to seek medical help should their condition worsen.**

1. **Previously healthy people (excluding pregnant women):** No antiviral treatment (symptomatic treatment only) **OR** oseltamivir (PO) if the clinician feels the patient is at serious risk of developing complications from influenza. Commence therapy within 48 hours of onset (or later at clinical discretion). See Table 1, section 1.3 for dosage.
2. **At risk population including pregnant women (but excluding severely immunosuppressed patients):** Oseltamivir (PO) (See Table 1, section 1.3 for dosage). Do not wait for laboratory confirmation. Treatment should be started as soon as possible, ideally within 48 hours of onset. There is evidence that treatment may reduce the risk of mortality up to five days after symptom onset. <sup>(13, 14, 17)</sup> Treatment after 48 hours is an off-label use of oseltamivir and clinical judgement should be used.
3. **Severely immunosuppressed patients:** Oseltamivir (PO) (See Table 1, section 1.3 for dosage). Treatment should start as soon as possible and ideally within 48 hours of symptom onset (or later at clinical discretion). Rapid emergence of oseltamivir resistance on treatment has been described in these patients and they should be monitored closely (**see Footnote 4**). In general influenza A (H1N1) pdm09 is considered to be a higher risk for the development of oseltamivir resistance whilst influenza A (H3N2) and influenza B are considered lower risk<sup>(5)</sup>. Clinicians may consider the use of zanamivir (inhaler) as first line therapy (ideally within 36 hours of symptom onset) in immunosuppressed patients with suspected or confirmed influenza A(H1N1)pdm09 based on clinical judgement (see Table 1, section 1.3 for dosage). In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).
4. **Suspected or confirmed oseltamivir resistant influenza in a patient who requires treatment:** Zanamivir (inhaler). Treatment should be started as soon as possible and ideally within 48 hours of symptom onset for adults and within 36 hours for children.

---

<sup>4</sup> **Footnote 3:** Oseltamivir resistance sometimes within one week of treatment initiation has been reported, particularly among immunocompromised patients with influenza A(H1N1) pdm09 <sup>(16, 18)</sup> Infection prevention and control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses.



- 5. Management of patients for whom zanamivir is indicated, who are unable to administer inhaled zanamivir:** Some patients who would normally receive inhaled zanamivir are unable to use it, either due to underlying severe respiratory disease or inability to effectively administer the inhaler (including children less than 5 years of age for whom zanamivir is unlicensed).
- a. Patients who are severely immunosuppressed and cannot take inhaled zanamivir should receive oseltamivir PO. As they are at increased risk of developing oseltamivir resistant influenza, they should be reviewed clinically to assess response to therapy.
  - b. Patients who have suspected or confirmed oseltamivir resistant infection and cannot take inhaled zanamivir should be considered for IV zanamivir. This decision will always be based on clinical judgement.
  - c. Zanamivir is licensed for intravenous (IV) administration in Ireland and approved for reimbursement by the Health Services Executive for the following indication: - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged  $\geq 6$  months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see [HPRA website](#)
  - d. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

## **Section 1.2: Treatment of adults and children with complicated influenza**

**All patients with complicated influenza should receive treatment, usually in hospital. Rapid testing for respiratory viruses including influenza virus is recommended for all patients fulfilling the clinical criteria for complicated infection. Treatment should be started as early as possible. Do not wait for laboratory confirmation of influenza virus infection.**

### **Note:**

1. Ensure that appropriate infection prevention and control precautions are applied to all patients. See [HPSC website](#).
2. Previous influenza immunisation does not exclude influenza as a possible diagnosis.
3. The duration of therapy depends on the clinical response.
4. Test for antiviral resistance in patients who do not respond after five days of treatment.

The following recommendations include the use of IV zanamivir.

**First line treatment:** Oseltamivir PO or NG (see exceptions below). There is evidence that PO/NG oseltamivir is adequately absorbed in critical illness at standard doses. <sup>(19)</sup>

**Second line treatment:** If there is a poor clinical response to first line treatment or if there is poor gastrointestinal absorption, use zanamivir. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot use a zanamivir inhaler may be considered for IV zanamivir. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

Zanamivir is licensed for intravenous (IV) **administration** in Ireland and approved for reimbursement by the Health Services Executive **for the following indication:** - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged  $\geq 6$  months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see [HPRA website](#)

## Exceptions:

### **Severely immunosuppressed patients:**

1. **First line treatment:** Oseltamivir PO or NG. Treatment should be started as soon as possible. Arrange influenza A subtype testing by the NVRL and monitor clinical condition closely.
2. Rapid emergence of oseltamivir resistance on treatment has been described in these patients and they should be monitored closely (see footnote 5). Resistance to oseltamivir has been described in infections from influenza A(H1N1)pdm09 but not in those from influenza A(H3) or influenza B to date (personal communication with NVRL). **Clinicians may consider the use of zanamivir as first line therapy in immunosuppressed patients with suspected or confirmed influenza A(H1N1)pdm09 based on clinical judgement.** In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance.
3. **Second line treatment:** If there is a poor clinical response to first line treatment, consider use of zanamivir and test for oseltamivir resistance. Ensure that appropriate infection prevention and control precautions are applied to these patients see [HPSC website](#).

Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot may be considered for IV zanamivir. IV zanamivir based on clinician's judgment may be considered for patients who: (a) have multi-organ involvement, or (b) require intensive care. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care) and used in accordance with the SmPC available at [HPRA website](#)

### **Suspected or confirmed oseltamivir resistance (e.g. contact of known oseltamivir resistant case (see footnote 6):**

1. **Do not use oseltamivir.**
2. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot may be considered for IV zanamivir. IV zanamivir based on the clinician's judgement may be considered for patients who have multi-organ involvement or require intensive care in accordance with the recommendations of the SmPC available on the [HPRA website](#)

## **Section 1.3: Antiviral dosage and schedules for treatment**

The recommended duration of antiviral treatment is 5 days. <sup>(5, 20)</sup> However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who completed 5- or 7-day courses of oseltamivir. <sup>(5, 38)</sup> Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunosuppressed patients. The manufacturer of oseltamivir recommends a longer treatment course of 75mg PO twice daily for 10 days for immunosuppressed patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.

---

<sup>5</sup> Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among immunocompromised patients with influenza A(H1N1)pdm09. <sup>(18)</sup> Infection prevention and control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses

<sup>6</sup> Sporadic oseltamivir resistant influenza A(H1N1)pdm09 has been identified including rare episodes of limited transmission; however the public health impact has been limited to date. <sup>(16, 18)</sup>

**Table 1: Antiviral treatment dosages and schedules for treatment**

Treatment	Premature (less than 36 weeks post conceptual age)	0-12 months (36 weeks post conceptual age or greater)	>1-12 years: Dose according to weight below:				Adults (≥ 13 years) <sup>1</sup>
			10-15kg	>15-23 kg	>23-40 kg	>40kg	
Oseltamivir PO	1mg/kg/dose every 12 hours <u>Unlicensed (see footnote 7)</u>	3mg/kg/dose every 12 hours	30mg every 12 hours	45mg every 12 hours	60mg every 12 hours	75mg every 12 hours	75mg Every 12 hours
Zanamivir (see footnote 8) inhaled (treatment course: 5 days)	Not licensed for use in children aged < 5 years old. For children aged ≥ 5 years of age, Dose: 10mg (two 5mg inhalations) every 12 hours						10mg (Two 5mg inhalations) every 12 hours

<sup>1</sup> If a person in this age group weighs 40kg or less, it is suggested that the >23-40kg dose for those aged >1-12 years is used.

Product information for oseltamivir is available on the [HPRA website](#)  
Product information for zanamivir is available on the [HPRA website](#)

### Oseltamivir

Oseltamivir oral suspension should be used for children and adults with swallowing difficulties. It is available as a 6 mg/mL oral suspension reconstituted from powder. The SmPC contains further information on extemporaneous formulation of a suspension from the capsules if oral suspension is not available.

### Zanamivir

Zanamivir is licensed for intravenous (IV) **administration** in Ireland and approved for reimbursement by the Health Services Executive **for the following indication:** - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see the [HPRA website](#) Recommendations for when to use IV zanamivir are included in section 1.2 above.

**For the use of oseltamivir and zanamivir in pregnancy and breastfeeding see Appendix A. For dosing in renal dysfunction, see Section 1.3.1.**

### Note on dosing for extremes of weight:

**Oseltamivir:** no dose adjustment is needed in obese patients. <sup>(24 - 26)</sup>

**IV zanamivir:** For adult patients (and adolescents with actual body weight 50kg or greater) the dose is not weight adjusted.

<sup>7</sup> This is an unlicensed use of oseltamivir and is based on evidence from literature and expert opinion <sup>(21 - 23)</sup>

<sup>8</sup> Zanamivir is approved for the treatment of persons aged ≥5 years in Ireland.

In adolescents with actual body weight less than 50kg and in children, the dose is weight adjusted. For specific dosing information please refer to the SmPC available on the [HPRA website](#)

### Section 1.3.1: Dosing in patients with renal dysfunction <sup>(5)</sup>

The information provided here on dosing in renal impairment and renal failure is intended specifically for consideration when patients have an existing history of chronic kidney disease (CKD) and renal failure results have been previously documented for the purpose of managing CKD. As with other groups, it is essential to initiate treatment as soon as possible.

The choice of dose in renal failure is complicated by the different measures available to describe degree of renal impairment, as well as a lack of specific data in some circumstances. Creatinine Clearance (CrCl) is used in this document as it is a more accurate measure upon which to make dosing recommendations and is congruent with the manufacturer’s prescribing information for both oseltamivir and zanamivir. The limitations for using eGFR are described in the British National Formulary (‘Prescribing in renal impairment’). CrCL can be estimated in adults by utilising the Cockcroft and Gault equation. Both eGFR and CrCL (using Cockcroft and Gault) assume the patient’s renal function is stable. Clinical judgement will be required where renal function is unstable (i.e. in acute renal failure).

It is recognised that eGFR may be more readily available at the outset of therapy. If this is the only value available then do not delay therapy and prescribe a dose according to eGFR (substituting eGFR for the CrCL figure in Table 2). Some patients may receive a larger oseltamivir dose as a result, but this is unlikely to be harmful as clinical experience reveals a wide margin of safety. The use of IV zanamivir is anticipated to only occur in hospitals, and as such all the data necessary to make a CrCL calculation will be available; do not use eGFR in this setting.

**Table 2: Recommended oseltamivir treatment dosing in renal dysfunction (adults and those aged 13 years and over) <sup>(5)</sup>**

<b>CrCL (ml/min)</b>	<b>Oseltamivir PO Treatment</b>
>60mL/min*	75mg every 12 hours
31-60 mL/min*	30mg every 12 hours
11-30mL/min*	30mg every 24 hours
≤10mL/min**	30mg ONCE
Haemo-dialysis (HD)*	30mg ONCE and then 30mg after every HD session
Peritoneal dialysis*	30mg ONCE
Haemo(dia)filtration** 1-1.8L/hr exchange rate	30mg every 24 hours
Haemo(dia)filtration** 1.9 – 3.6L/hr exchange rate	30mg every 12 hours
Haemo(dia)filtration** > 3.6L/hr exchange rate	75mg every 12 hours

**Source:** Summary of Product Characteristics (SmPC) updated October 2021. (\*) The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion.(++)<sup>(5)</sup>

**Note:** It is acknowledged that some of the advice for dosing in renal impairment presented in Table 2 may differ to the renal drug database; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer at the time of writing.

### **Section 1.3.2: Treatment of oseltamivir resistant influenza**

The same criteria as for non-resistant influenza infection apply in deciding whom to treat.

1. Previously healthy people with uncomplicated disease, or those who have recovered with or without oseltamivir, do not require treatment.
2. Those who require treatment should have zanamivir.
3. Those with uncomplicated influenza should receive inhaled zanamivir (authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland).
4. Those with complicated influenza may receive inhaled or IV zanamivir as is appropriate to their clinical condition (see section 1.2).
5. In the event of changes in the epidemiology or clinical aspects of drug resistant influenza during the season, HPSC will alert clinicians and provide updated advice.

### **Section 1.3.3: Management of influenza in critical care**

The principles are the same as for complicated influenza.

1. The first line therapy remains PO/NG oseltamivir and there is evidence that standard dose oseltamivir PO or NG is adequately absorbed even in critical illness.<sup>(19)</sup> Increasing the dosage is no longer recommended in patients who are severely ill with influenza A due to lack of evidence that it is any more effective.<sup>(27, 28)</sup> Specialist advice should be sought for dosage of patients critically ill with influenza B.
2. Zanamivir should be used when there is suspected poor gastrointestinal absorption or failure to respond to oseltamivir.
3. In intensive care, zanamivir may be given intravenously based on the clinician's judgement for situations such as multi-organ failure. The use of IV zanamivir should be supervised by a consultant in intensive care medicine and used in accordance with the recommendations as per the SmPC available on the [HPRA website](#)

## **Section 2: Post exposure prophylaxis**

Key points: <sup>(5)</sup>

- Chemoprophylaxis (oseltamivir/ zanamivir) may be considered for people in at risk groups who have had recent close contact with a person with influenza or influenza like illness (ILI) in the same household or residential setting when influenza is circulating in the community<sup>9</sup>.
- Chemoprophylaxis may be considered if the contact is not adequately protected by vaccination **OR** where the person has been exposed in the context of a local outbreak, regardless of vaccination status.
- Chemoprophylaxis should be commenced within 48 hours of the most recent exposure for oseltamivir and within 36 hours for zanamivir and is administered for 10 days after the most recent known exposure to a close contact known to have influenza.

Influenza vaccination and infection prevention and control practices are of utmost importance in the prevention of influenza, and are universally preferred over the administration of chemoprophylaxis. Antiviral medications with activity against influenza viruses are an important adjunct to these measures in the control of influenza. In randomised placebo-controlled trials, both oseltamivir and zanamivir were efficacious in the prevention of influenza illness among persons administered chemoprophylaxis after exposure to a household member or other close contact who had laboratory-confirmed influenza (zanamivir: 72-82%; oseltamivir: 68-89%). <sup>(29, 30)</sup> Both are recommended for antiviral chemoprophylaxis of influenza A and B.

Chemoprophylaxis should be reserved for those in at risk groups (see P. 5 of this guidance) who have had recent close contact (see footnote 10) with a person with influenza or influenza-like illness in the same household or residential setting when influenza is circulating in the community<sup>9</sup>. Previous influenza vaccination does not preclude the use of post exposure prophylaxis, in particular where localised outbreaks occur in residential care facilities (RCF). (see footnote 11)

As per UK National Institute of Clinical Excellence (NICE) guidance, prophylaxis should be issued if the contact is not adequately protected by vaccination - that is, in the situations outlined below:

- The vaccine is not well matched to the circulating strain (Refer to HPSC weekly influenza reports available on the [HPSC website](#))
- There has been fewer than 14 days between vaccination and symptom onset <sup>(5)</sup>

Use of post exposure prophylaxis may also be considered where:

- The individual has been exposed as part of a localised outbreak (such as in a residential care facility) regardless of vaccination status, as seasonal influenza vaccination may be less effective in older persons or the immunosuppressed. <sup>(5, 32)</sup>

Chemoprophylaxis is not routinely considered in at-risk groups who have been vaccinated against seasonal influenza at least 14 days prior to exposure, with the above exceptions.

**An alternative to chemoprophylaxis in some clinical settings may be to monitor persons exposed to an influenza case and commence antiviral treatment promptly if symptoms of influenza arise.** <sup>(5)</sup>

Clinical judgement should be exercised in individual cases. If a high-risk contact becomes symptomatic, ensure early commencement of antiviral treatment. Patients receiving chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop any signs of illness suggestive of influenza.

---

<sup>9</sup> : Rates above the ILI threshold combined with sentinel GP influenza positivity >10% indicate the likelihood that influenza is circulating in the community.

<sup>10</sup> Close contact is defined as having cared for or lived with a person who has confirmed, probable or suspect influenza or having been in a setting where there is a high likelihood of contact with respiratory droplets and/or body fluids of such a person, including having talked face-to-face with them. <sup>(31)</sup>

<sup>11</sup> See guidance re the management of influenza/ILI outbreaks in residential care facilities at <http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Guidance/ResidentialCareFacilitiesGuidance/>



Decisions on whether to administer antivirals for chemoprophylaxis should be made on a case-by-case basis, taking into account:

1. the exposed person's risk of developing influenza complications
2. the type and duration of contact
3. clinical judgement <sup>(7)</sup>

Generally, post exposure chemoprophylaxis should be commenced within 48 hours of the most recent exposure for oseltamivir and within 36 hours for zanamivir and is administered for 10 days after the most recent known exposure to a close contact known to have influenza. Commencement of the administration of chemoprophylaxis >48 hours for oseltamivir and >36 hours for zanamivir is an off-label use and should be based on specialist advice only.

## **Section 2.1: Chemoprophylaxis in specific settings/ risk groups**

- **Residential care facilities (RCF):**

Specialist advice should be sought regarding chemoprophylaxis in these situations. See guidance on the management of influenza in residential care facilities available [on the HPSC website](#).

- **Pregnant and postpartum women:**

Post-exposure antiviral chemoprophylaxis can be considered for pregnant women and women who are up to two weeks postpartum who have had close contact (see footnote12) with someone likely to have been infectious with influenza. Clinical judgement should be exercised in individual cases to determine if the benefit outweighs the risk. Pregnant women and women who are up to two weeks postpartum who are given post-exposure chemoprophylaxis should be informed that the chemoprophylaxis lowers, but does not eliminate, the risk of influenza and that protection stops when the medication course is stopped. <sup>(31)</sup> See [HPSC website](#).

An alternative approach for pregnant women who have had close contact with a patient with laboratory confirmed influenza is to provide information on the early signs and symptoms of influenza, and advise them to contact their doctor immediately for evaluation and possible early antiviral treatment if clinical signs or symptoms develop following a risk assessment.

- **Neonates exposed to mothers who develop seasonal influenza in the peripartum period:**

As pregnancy confers increased risk of complicated influenza, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered, commensurate with recommendations outlined earlier in this guidance document. A particular clinical challenge arises with regard to the neonate if a pregnant woman develops laboratory confirmed seasonal influenza shortly before the onset of labour. The potential mode of transmission to the neonate in such a scenario is via direct contact with the infected respiratory secretions of the mother rather than via breastmilk.

There are limited data regarding seasonal influenza infection in neonates. The Influenza Clinical Information network (Flu-CIN) study reported severe outcomes in 9.3% of children aged less than 12 months in the UK who were hospitalised with influenza A(H1N1)pdm09 during the 2009-2010 pandemic. <sup>(40)</sup>

The Summary of Product Characteristics (SmPC) for oseltamivir oral suspension states that the medicine can be used for post-exposure prevention of influenza in infants aged over 1 year and for post exposure prophylaxis in infants during a pandemic influenza outbreak in those less than 1 year of age. Treatment of

---

<sup>12</sup> Close contact is defined as having cared for or lived with a person who has confirmed, probable or suspect influenza or having been in a setting where there is a high likelihood of contact with respiratory droplets and/or body fluids of such a person, including having talked face-to-face with them. <sup>(31)</sup>



seasonal influenza in children, including full term neonates, is however, specified in the SmPC for oseltamivir capsules and powder for oral suspension. Zanamivir inhaler is not licensed for treatment or prophylaxis in children less than 5 years of age.

There are three potential options which may be considered by mothers and clinicians in relation to neonates:

1. Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, which may be an unlicensed indication if used outside a pandemic influenza outbreak  
As prophylaxis reduces but does not eliminate the risk of infection, infants should be closely monitored for signs and symptoms of Influenza. The mother should be advised of measures to reduce risk of transmission including respiratory hygiene and cough etiquette, use of a facemask during close contact, including breast-feeding, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.
2. Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after symptom onset.  
Disadvantages for the neonate would include not being able to benefit from breastfeeding-related transfer of immune factors and nutrients. These considerations should be included in the discussion with the mother. Women should be encouraged to express breastmilk so that the neonate can receive the benefits of breastmilk, and to maintain the mother's milk supply in order that breastfeeding can continue once mother and baby are reunited.
3. No prophylaxis for the neonate and no separation of neonate and mother.  
This will require careful monitoring for symptoms of influenza, a discussion in advance with the mother about prompt antiviral treatment of the neonate, and advance arrangements for rapidly accessing oseltamivir oral suspension if required (as this is more readily available via hospital pharmacies than community pharmacies). There should also be consideration of laboratory testing of a symptomatic neonate, as per existing local arrangements. In this situation, the mother should be advised of measures to reduce risk of transmission, including respiratory hygiene and cough etiquette, use of personal protective equipment such as a facemasks, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

Decisions regarding the most appropriate course of action should be made on a case-by-case basis and are likely to involve detailed discussion between the mother and physician regarding the relative advantages and disadvantages of each potential option. This advice does not constitute a specific endorsement of the routine use of oseltamivir oral suspension for prophylaxis in neonates, but recognises that this may occur as an off-label use in specific circumstances. Such clinical scenarios highlight the importance of seasonal influenza vaccination of pregnant women; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England. <sup>(41, 42)</sup>

## **Section 2.2: Selection of antivirals for post exposure chemoprophylaxis**

**Table 3: Selection of antivirals for post-exposure chemoprophylaxis**

	<b>Exposed to influenza A or B</b>	<b>Exposed to suspected or confirmed oseltamivir resistant influenza</b>
<b>Previously healthy (excluding pregnant women)</b>	No prophylaxis.	No prophylaxis
<b>At risk of complicated influenza (including pregnant women, but excluding severely immunosuppressed patients and excluding children aged &lt; 5 years old)</b>	<u>Oseltamivir PO every 24 hours for 10 days</u> if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	<u>Zanamivir INH every 24 hours for 10 days</u> if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only.
<b>Severely immunosuppressed patients (excluding children aged &lt; 5 years old)</b>	<u>Oseltamivir PO every 24 hours for 10 days</u> if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	<u>Zanamivir INH every 24 hours for 10 days</u> if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only. If unable to administer zanamivir INH monitor closely and begin treatment promptly if ILI symptoms develop.
<b>Children aged &lt; 5 years in at risk group including severely immunocompromised children</b>	<u>Oseltamivir PO every 24 hours for 10 days</u> if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	<u>Discuss with specialist.</u>

## Section 2.3: Antiviral dosage and schedules for post exposure chemoprophylaxis

**Table 4: Antiviral dosage and schedules for chemoprophylaxis**

Prophylaxis	Premature (< 36 weeks post conceptual age)	0-≥12 months (36 weeks post conceptual age or greater)	>1-12 years: Dose according to weight below				Adults (≥13 years) <sup>1</sup>
			10-15kg	>15-23kg	>23-40kg	>40kg	
Oseltamivir PO (prophylaxis course: 10 days)	See below (see footnote 13)	3 mg/kg every 24 hours <sup>2</sup>	30 mg every 24 hours	45 mg every 24 hours	60 mg every 24 hours	75 mg every 24 hours	75 mg every 24 hours
Zanamivir INH (prophylaxis course: 10 days)	Not licensed in children aged <5 years old Children aged ≥5 years : 10 mg (two 5mg inhalations) every 24 hours						10 mg (two 5 mg inhalations) every 24 hours

<sup>1</sup> If a person in this age group weighs 40 kg or less, it is suggested that the >23-40 kg dose for those aged >1-12 years is used.

<sup>2</sup> Only indicated in those less than 1 year of age during a pandemic influenza outbreak (SmPC)

### Oseltamivir

Oseltamivir oral suspension should be used for children and adults with swallowing difficulties. It is available as a 6 mg/mL oral suspension reconstituted from powder. Its licensed indication for post exposure prevention in infants less than 1 year is only for use during a pandemic influenza outbreak. However, its use is supported by the BNF for children in this age category. The SmPC contains further information on extemporaneous formulation of a suspension from the capsules if oral suspension is not available.

### Zanamivir

Inhaled zanamivir is not licensed for children less than five years of age and is unlikely to be an effective delivery route in this age group. In addition, patients with severe underlying respiratory disease may be unable to use the inhaler effectively.

Severely immunosuppressed children under five years of age and all other severely immunosuppressed patients who cannot use the zanamivir inhaler and require prophylaxis after exposure to currently circulating antiviral sensitive strains of influenza should receive oral oseltamivir with advice to seek medical attention if they become unwell (Table 3).

### Section 2.3.1: Dosing in patients with renal dysfunction <sup>(5)</sup>

General considerations about prescribing for renal impairment discussed in the treatment section (section 1.3.1) may also be applicable when prescribing for prophylaxis, except that the dosage of oseltamivir in Table 5 should be used.

**Table 5: Recommended oseltamivir prophylaxis dosing in renal impairment (adults and those aged 13 years or over)**

<sup>13</sup> Although it may be possible to provide half of the daily treatment dose for 10 days there is currently no publicly available dosing information for oseltamivir prophylaxis in pre-term infants so it is outside the product licence.

CrCL (ml/min)	Oseltamivir PO prophylaxis
>60mL/min*	75mg every 24 hours
31-60 mL/min*	30mg every 24 hours
11-30mL/min*	30mg every 48 hours
≤10mL/min <sup>++</sup>	30mg ONCE, repeated after 7 days
Haemo-dialysis (HD)*	30mg ONCE and then 30mg after every second HD session
Peritoneal dialysis*	30mg ONCE, repeated after 7 days
Haemo(dia)filtration <sup>++</sup> 1-1.8L/hr exchange rate	30mg every 48 hours
Haemo(dia)filtration <sup>++</sup> 1.9-3.6L/hr exchange rate	30mg every 24 hours
Haemo(dia)filtration <sup>++</sup> >3.6L/hr exchange rate	75mg every 24 hours

**Source:** Summary of Product Characteristics updated October 2021. (\*). The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion (++)<sup>(5)</sup>

**Note:** It is acknowledged that some of the advice for dosing in renal impairment presented here may differ to the renal drug database; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer, at the time of writing.

No difference in prophylaxis dosing for high flux and low flux intermittent haemodialysis (HD) is recommended due to a lack of published clinical data on oseltamivir carboxylate levels in high flux intermittent HD patients; this advice is expert opinion based on information on pore size, OC molecule size and likely length of HD sessions.

For dose adjustment in renal impairment in children aged less than 13 years, adjust the oseltamivir dose as per the oseltamivir chapter in the BNF for children:  
<https://bnfc.nice.org.uk/drug/oseltamivir.html#renalImpairment>

## **Appendix A: Use of antivirals in pregnancy, breastfeeding, hepatic dysfunction**

	<b>Liver dysfunction</b>	<b>Renal dysfunction</b>
<b>Oseltamivir PO</b>	Standard dosing	<b>See product information for oseltamivir available on the <a href="#">HPRA website</a></b>
<b>Zanamivir INH</b>	Standard dosing	See product information for zanamivir available on the <a href="#">HPRA website</a>
<b>Zanamivir solution IV</b>	Standard dosing	See product information for zanamivir IV available on the <a href="#">HPRA website</a>

### **Use in Pregnant women**

Antivirals have been recommended for pregnant women due to the adverse clinical outcomes that have been observed for influenza infection in this group. Oseltamivir remains the first line option for the vast majority of pregnant women with influenza, including during seasons that are dominated by influenza A(H1N1)pdm09. For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (i.e. rapid diagnostics) and antiviral treatment should be discussed with a local infection specialist. Oseltamivir is generally well tolerated in patients with influenza, but side effects can occur. There are no data suggesting tolerability differs between pregnant and non-pregnant adults. Recent studies suggest there is no evidence of harm in pregnant women treated with oseltamivir or zanamivir. <sup>(33, 34)</sup>

**The Summary of Product Characteristics (SmPC) for oseltamivir states the following:** "Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor fetoneonatal toxicity by oseltamivir. However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza. Animal studies do not indicate reproductive toxicity." <sup>(35)</sup>

"The use of Tamiflu [oseltamivir] may be considered during pregnancy if necessary and after considering the available safety and benefit information and the pathogenicity of the circulating influenza virus strain." <sup>(35)</sup>

**The Summary of Product Characteristics (SmPC) for zanamivir inhaler states the following:** "Systemic exposure to zanamivir is low following administration by inhalation; however, there is no information on placental transfer of zanamivir in humans. There is a limited amount of data (less than 300 pregnancy outcomes) from the use of zanamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Relenza [zanamivir] during pregnancy, unless the clinical condition of the woman is such that the potential benefit to the mother significantly outweighs the possible risk to the foetus." <sup>(36)</sup>

**Use during breastfeeding**

The UK Drugs in Lactation Advisory Service (UK DILAS) has published advice on the use of oseltamivir and zanamivir while breastfeeding: <https://www.sps.nhs.uk/articles/oseltamivir-or-zanamivir-can-mothers-breastfeed-after-treatment-for-influenza-2/>

## **Appendix B: Antiviral medications authorised by the European Medicines Agency but not approved for use in the HSE**

The following influenza treatments are authorised by the European Medicines Agency but are not approved for use in the HSE or marketed in Ireland. Specialist advice should always be sought prior to initiating these agents.

### **Baloxavir marboxil**

- Baloxavir is a novel, single dose, oral antiviral agent that demonstrates antiviral activity against influenza A and B. It is a cap-dependent endonuclease inhibitor and, as such, has a different mechanism of action from the neuraminidase inhibitors.
- Baloxavir is authorised for use by the EMA for the treatment of uncomplicated influenza in patients aged 12 year and above and for post-exposure prophylaxis of influenza in individuals aged 12 year and above. A single dose should be taken as soon as possible within 48 hours of symptom onset or following close contact with an individual known or suspected to have influenza.
- Baloxavir dosing by bodyweight and other product information can be found on the SmPC on the [HPRA website](#)



## Appendix C: Frequently asked questions <sup>(5)</sup>

### **Q. When should I consider extending antiviral therapy beyond 5 days?**

The recommended duration of antiviral treatment is 5 days. <sup>(20)</sup> However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and ‘rebound’ of previously undetectable viral RNA have been described in patients with severe influenza who completed 5- or 7-day courses of oseltamivir. <sup>(37)</sup> Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunosuppressed patients. The manufacturer of oseltamivir recommends a longer treatment course for 10 days for immunosuppressed patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.

### **Q. What is meant by “poor clinical response to first line treatment”?**

A poor clinical response in a patient receiving first line antiviral medication may constitute any of the following:

- No clinical improvement
- Progressive lower respiratory tract signs or symptoms
- New or progressive multi-organ dysfunction

Potential explanations for a poor clinical response include, but are not limited to, antiviral resistance. Antiviral resistance has been rare in recent influenza seasons, but is most frequently observed in cases of infection with influenza A(H1N1)pdm09 as opposed to other seasonal influenza viruses. Additional risk factors for antiviral resistance include severe immunosuppression.

Absence of clinical improvement, or clinical deterioration, may also be caused by the natural progression of acute lung injury and the inflammatory response that accompanies influenza infection, or by secondary infection, e.g. bacterial co-infection. Therefore, decisions regarding the presence or absence of a “poor clinical response”, and the underlying aetiology, must be made by the treating physician on a case-by-case basis, guided by these considerations.

### **Q. Which groups of patients are at risk of antiviral resistance?**

Among patients in receipt of influenza antiviral treatment, immunocompromised individuals and young children are at increased risk of harbouring viruses that demonstrate antiviral resistance. This may be explained by prolonged duration of infection and/or higher viral burden compared to other patient groups. Rapid emergence of oseltamivir resistance (as early as 48 hours after initiation of treatment) has been described, particularly in severely immunocompromised individuals. <sup>(38)</sup>

Between July 2009 and April 2010, 285 cases of oseltamivir-resistant pandemic influenza A(H1N1)pdm09 infection were reported globally, including 45 cases in the UK. Of these UK cases, data regarding underlying medical conditions were available for 28. Of these 28 cases, 21 (75%) were immunosuppressed, the most common underlying condition being leukaemia (11 of 21). <sup>(39)</sup>

### **Q. If zanamivir resistance is suspected, should I switch to oseltamivir?**

No. Recent antiviral resistance surveillance data demonstrate that oseltamivir resistance remains more common than zanamivir resistance. Several mutations that confer resistance to zanamivir are also associated with resistance or reduced susceptibility to oseltamivir. If zanamivir resistance is suspected (e.g. as a causative factor in poor clinical response to antiviral treatment), then zanamivir treatment should be continued and urgent testing for resistance should be undertaken. Advice should be sought from local infection specialists, e.g. consultant medical virologist.

**Q. What is the role of repeat sampling and laboratory testing in patients undergoing treatment with antiviral medication?**

It can be challenging to assess clinical improvement in specific patient groups that may demonstrate atypical or minimal clinical signs and symptoms, e.g. immunosuppressed patients, or may be unable to describe their symptoms, e.g. unconscious/ventilated patients. In such patients with confirmed influenza infection who are receiving antiviral therapy, repeat/“follow-up” sampling for detection of viral RNA by polymerase chain reaction (PCR) may be considered under the following circumstances:

- Clinical deterioration or unresolving illness despite at least 5 days of antiviral medication, potentially necessitating a prolonged duration of antiviral treatment
- Development of influenza illness while in receipt of prophylactic-dose antivirals; either test at time of symptom onset or test according to clinical deterioration

Repeat sampling is not routinely recommended in patient groups or clinical contexts beyond those described above.

When repeat testing has been performed due to suspected treatment failure, antiviral resistance testing on any positive sample should be considered, and is recommended if the patient is immunosuppressed. Comparing estimated viral load in the initial and repeat samples may be helpful in assessing the antiviral effect.

If oseltamivir resistance is suspected and further treatment is required, consider switching to zanamivir without awaiting results of resistance testing. Treatment interruption should be avoided as it may promote development of antiviral resistance.

If repeat/follow-up testing yields positive results, the need for ongoing IPC measures for inpatients must be considered by healthcare workers (HCW).

In some cases repeat testing may be undertaken when considering transfer of a patient with laboratory confirmed influenza from an isolation room to an open ward/unit. In this scenario, repeat testing requests should be discussed with the testing laboratory, as an immunofluorescence assay (IFA) may provide more useful information than PCR testing. This is because PCR testing detects residual viral RNA and is likely to remain positive in patients with influenza who are no longer infectious, but IFA only detects viable virus and is likely to be negative in patients who are no longer infectious, providing support for decisions to transfer such patients to an open ward/unit.

**Q. Should unvaccinated hospital-based healthcare workers (HCW) with no underlying illness be offered antiviral chemoprophylaxis?**

In the hospital setting, chemoprophylaxis is only recommended for at-risk groups and should not be considered as an alternative to vaccination. The use of prophylactic antivirals in individuals who are not in risk groups as an influenza outbreak control measure in the hospital setting is not recommended. HCWs who are not in risk groups may continue to work, using appropriate personal protective equipment (PPE), and should be advised to immediately report any signs or symptoms of illness. They should be promptly excluded from work if they develop any signs or symptoms of influenza/ILI. It is imperative that the importance of annual seasonal influenza vaccination, and non-attendance at work if unwell, is emphasised to HCWs.

**Q. What is the role of previous laboratory-confirmed influenza when a person presents with a new episode of ILI in the same influenza season?**

The two episodes of infection should be considered separately and treatment prescribed, if indicated, on both occasions. It is entirely possible that the first infection is with an influenza A virus and the subsequent infection is with an influenza B virus, or vice versa, or subsequent infection may be with a different A/subtype or B/lineage virus, or different circulating respiratory virus, so there would be no protective effect from the first exposure.

**Q. Should antiviral medication be offered in neonates exposed to mothers with seasonal influenza?**

As pregnancy confers increased risk of complicated influenza, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered, commensurate with recommendations outlined earlier in this guidance document. A particular clinical challenge arises with regard to the neonate if a pregnant woman develops laboratory confirmed seasonal influenza shortly before the onset of labour. The potential mode of transmission to the neonate in such a scenario is via direct contact with the infected respiratory secretions of the mother rather than via breastmilk.

There are limited data regarding seasonal influenza infection in neonates. The Influenza Clinical Information network (Flu-CIN) study reported severe outcomes in 9.3% of children aged less than 12 months in the UK who were hospitalised with influenza A(H1N1)pdm09 during the 2009-2010 pandemic. <sup>(40)</sup>

The Summary of Product Characteristics (SmPC) for oseltamivir oral suspension states that the medicine can be used for post-exposure prevention of influenza in infants aged over 1 year and for post exposure prophylaxis in infants during a pandemic influenza outbreak in those less than 1 year of age. Treatment of seasonal influenza in children, including full term neonates, is however, specified in the SmPC oseltamivir for capsules and oral suspension. Zanamivir inhaler is not licensed for treatment or prophylaxis in children less than 5 years of age.

There are three potential options which may be considered by mothers and clinicians in relation to neonates:

1. Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, which may be an unlicensed indication if used outside a pandemic influenza outbreak.

As prophylaxis reduces but does not eliminate the risk of infection, infants should be closely monitored for signs and symptoms of Influenza. The mother should be advised of measures to reduce risk of transmission including respiratory hygiene and cough etiquette, use of a facemask during close contact and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

2. Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after symptom onset.

Disadvantages for the neonate would include not being able to benefit from breastfeeding-related transfer of immune factors and nutrients. These considerations should be included in the discussion with the mother. Women should be encouraged to express breastmilk so that the neonate can receive the benefits of breastmilk, and to maintain the mother's milk supply in order that breastfeeding can continue once mother and baby are reunited.

3. No prophylaxis for the neonate and no separation of neonate and mother.

This will require careful monitoring for symptoms of influenza, a discussion in advance with the mother about prompt antiviral treatment of the neonate, and advance arrangements for rapidly accessing oseltamivir oral suspension if required (as this is more readily available via hospital pharmacies than community pharmacies). There should also be consideration of laboratory testing of a symptomatic neonate, as per existing local arrangements. In this situation, the mother should be advised of measures to reduce risk of transmission, including respiratory hygiene and cough etiquette, use of personal protective equipment such as a facemasks, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

Decisions regarding the most appropriate course of action should be made on a case-by-case basis and are likely to involve detailed discussion between the mother and physician regarding the relative advantages and disadvantages of each potential option. This advice does not constitute a specific endorsement of the routine use of oseltamivir oral suspension for prophylaxis in neonates, but recognises that this may occur as an off-label use in specific circumstances. Such clinical scenarios highlight the importance of seasonal influenza vaccination of pregnant women; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England. <sup>(41,42)</sup>

**Q. Should diagnostic sampling for influenza be performed when commencing antiviral post-exposure prophylaxis?**

When a decision has been made to administer antiviral prophylaxis to immunosuppressed and critically ill patients who are identified as close contacts of a confirmed case, diagnostic sampling of these contacts for influenza virus detection is recommended before or at the time of commencing antiviral prophylaxis. Please note this only pertains to the afore mentioned groups of patients and is not routinely undertaken.

This is based on expert advice as symptoms and signs of influenza may be absent, minimal or atypical in these patient groups, or may be difficult to assess due to their clinical status. It is important to note that prophylactic doses of antivirals can promote antiviral resistance in patients already infected with influenza virus, especially when there is underlying immunosuppression.

While prophylaxis should not be postponed while the results of influenza testing are awaited, influenza virus testing should be expedited. If testing demonstrates that a patient in receipt of a prophylactic dose of an antiviral is actually infected with influenza virus, then prophylaxis should be stopped and treatment-dose antivirals should be commenced immediately. Any prophylactic doses received should not be counted when determining the duration of treatment-dose antivirals.

Following the positive influenza test result, physicians and HCWs should assess the need to continue transmission based precautions beyond the recommended period of seven days on a case by case basis as it is not possible to predict duration of viral shedding for this cohort of patients. Cessation of transmission-based precautions will need to be considered locally by an infection specialist, on a case by case basis.

**Q. Should the standard treatment dose of oseltamivir be doubled (“double-dosing”) when treating patients with severe illness caused by seasonal influenza infection?**

An increase in dosage is no longer recommended in patients with severe illness caused by influenza A virus infection, due to a lack of evidence that it is any more effective than standard dosing. <sup>(43)</sup>

Although it has been previously reported that higher inhibitory concentrations of oseltamivir carboxylate are required to produce an effect on Influenza B in in-vitro tests <sup>(43,44)</sup>, there is insufficient evidence to support double-dosing in patients with Influenza B in vivo. <sup>(45)</sup>

## References

1. Cochrane Acute Respiratory Infections Group (2014). Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract>
2. Centers for Disease Prevention and Control (USA) (April 10th 2014). CDC Recommendations for Influenza Antiviral Medications Remain Unchanged. [https://www.cdc.gov/media/haveyouheard/stories/Influenza\\_antiviral2.htm](https://www.cdc.gov/media/haveyouheard/stories/Influenza_antiviral2.htm)
3. Centers for Disease Prevention and Control (USA) (January 16th 2018). Prompt Use of Antivirals is Key this Flu Season. <https://www.cdc.gov/features/flu-antivirals/index.html>
4. Infectious Disease Society of America. (April 2014). Statement by the Infectious Disease Society of America (IDSA) on the recent publication on "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children". <https://www.healio.com/pediatrics/influenza/news/online/%7Ba0c96499-e0c3-409a-9d59-538131ed73c0%7D/controversy-surrounds-recent-papers-on-use-of-neuraminidase-inhibitors-for-influenza>
5. Public Health England (November 2021). Guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza version 11. Available at: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1037465/ukhsa-guidance-antivirals-influenza-11v4.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1037465/ukhsa-guidance-antivirals-influenza-11v4.pdf)
6. European Centre for Disease Prevention and Control. ECDC Scientific Advice. Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza. Review of recent systematic reviews and meta-analyses. ECDC, August 14<sup>th</sup> 2017. Available at <https://ecdc.europa.eu/en/publications-data/expert-opinion-neuraminidase-inhibitors-prevention-and-treatment-influenza-review>
7. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: Recommendations of the Advisory Committee on Immunisation Practices (ACIP). Morbidity and Mortality Report, Recommendations and Reports/Vol 60/No. 1. January 21<sup>st</sup> 2011. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>
8. National Immunisation Advisory Committee. Immunisation Guidelines for Ireland, 2013. Chapter 11, Influenza (Updated October 2021). <http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter11.pdf>
9. Scientific Advisory Group for Emergencies (SAGE) (2020). Summary of the effectiveness and harms of different non-pharmaceutical interventions, 21 September 2020 Available at: [S0769\\_Summary\\_of\\_effectiveness\\_and\\_harms\\_of\\_NPIs.pdf](S0769_Summary_of_effectiveness_and_harms_of_NPIs.pdf) ([publishing.service.gov.uk](https://assets.publishing.service.gov.uk))
10. Academy of Medical Sciences. (2020) 'Preparing for a challenging winter 2020 to 2021' 14 July 2020 Available at: <https://acmedsci.ac.uk/file-download/51353957>

11. Stowe J, Tessier E, Zhao H, et al. Interactions between SARS-CoV-2 and influenza, and the impact of coinfection on disease severity: a test-negative design. *International Journal of Epidemiology*. 2021 Aug;50(4):1124-1133.
12. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP et al. Antivirals for treatment of influenza; a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 2012 Apr 3; 156(7):512-524.
13. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for adults: a meta-analysis of randomised controlled trials. *The Lancet*; Volume 385, No. 9979, p1729-1737, 2 May 2015.
14. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM et al. Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010 April 21; 303(15): 1517-25.
15. Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. *Clin Infect Dis*. 2011 Feb 15; (52)4:457-65.
16. Centers for Disease Control and Prevention. Oseltamivir-resistant novel influenza A(H1N1) virus infection in two immunosuppressed patients-Seattle, Washington, 2009. *MMWR* 2009;58:893-6.
17. Muthuri et al (2014). Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A (H1N1) pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respirator Medicine*; 2014 May ; 2(5): 395-404.
18. Le QM, Wertheim HF, Tran ND et al. A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza. *N Engl J Med* 2010;362:86-7.
19. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *CMAJ* 2010;182:357-63.
20. Harper SA, Bradley JS, England JA et al. Seasonal influenza in adults and children- diagnosis, treatment and chemoprophylaxis and institutional outbreak management: clinical guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1003-32.
21. Acosta EP, Jester P, Gal P et al (2010). Oseltamivir Dosing in Influenza in Premature Neonates. *J Infect Dis*; 2010, 202(4): 563-566.  
<https://www.ncbi.nlm.nih.gov/pubmed/20594104>
22. McPherson C, Warner B, Hunstad DA et al. (2012). Oseltamivir Dosing in Premature Infants. *J Infect Dis*. 2012, 206(6): 847-850. <https://www.ncbi.nlm.nih.gov/pubmed/22807525>
23. Centers for Disease Control and Prevention (2021). Influenza Antiviral Medications: Summary for Clinicians. <https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>



24. Pai MP, Lodise TP Jr (2011). Oseltamivir and oseltamivir carboxylate pharmacokinetics in obese adults: dose modification for weight is unnecessary. *Antimicrob Agents Chemother.* 2011; 66:2083-2091. <http://www.ncbi.nlm.nih.gov/pubmed/21930881>
25. Thorne-Humphry LM et al. (2011). Oseltamivir pharmacokinetics in morbid obesity (OPTIMO trial). *J Antimicrob Chemother* 2011;66:2083-2091. <https://www.ncbi.nlm.nih.gov/pubmed/21700623>
26. Jittamlal P et al. (2014). Pharmacokinetics of orally administered oseltamivir in healthy obese and non-obese Thai subjects. *Antimicrob Agents Chemother* 2014 Volume 58 Number 3: 1615-1621. <http://www.ncbi.nlm.nih.gov/pubmed/24366750>
27. Lee et al (2013). A prospective intervention study on higher dose oseltamivir treatment in patients hospitalised with influenza A and B infections. *Clinical Infectious Diseases.* 2013 Dec: 57(11): 1511-9.
28. South East Asia Infectious Disease Research Network (2013). Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomized controlled trial. *British Medical Journal.* 2013 May 30: 346.
29. Welliver R, Monto AS, Carewicz O et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001;285:748-54.
30. Monto AS, Pichichero ME, Blanckenberg SJ et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002;186:1582-8.
31. Centers for Disease Control and Prevention (2021). Recommendations for Obstetric Health Care Providers related to use of antiviral medications in the treatment and prevention of influenza. [http://www.cdc.gov/flu/professionals/antivirals/avrec\\_ob.htm](http://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm)
32. National Institute for Health and Care Excellence (2008). Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza. <http://guidance.nice.org.uk/TA158>
33. Dunstan HJ, Mill AC, Stephens S, Yates LM, Thomas SH (2014). Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: a national prospective surveillance study *BJOG.* 2014 Jun;121(7):901-6. <https://www.ncbi.nlm.nih.gov/pubmed/24602087>
34. Wollenhaupt M, Chandrasekaran A, Tomianovic D (2014). The safety of oseltamivir in pregnancy: an updated review of post-marketing data. *Pharmacoepidemiol Drug Saf.* 2014 Oct;23(10):1035-42. <http://www.ncbi.nlm.nih.gov/pubmed/24995623>
35. Roche Products Limited (2021) Summary of Product Characteristics for Tamiflu <https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=tamiflu&field=>
36. GlaxoSmithKline (2019) SmPC for Relenza 5mg/dose inhalation powder <https://www.hpra.ie/homepage/medicines/medicines-information/find-a->



medicine/results/item?pano=PA1077/011/001&t=Relenza%205mg/dose,%20inhalation%20 powder,%20pre-dispensed

37. Lee, N, Chan PKS, Wong CK, et al (2011) Viral clearance and inflammatory response patterns in adults hospitalised for pandemic 2009 influenza A(H5N1) virus pneumonia. *Antiviral Therapy* 2011; 16: 237-247  
<https://www.intmedpress.com/serveFile.cfm?sUID=818bbc6c-5093-4a1b-b047-e7274387a7e2>
38. Inoue M, Barkham T, Leo Y-S, et al (2010) Emergence of Oseltamivir-Resistant Pandemic (H1N1) 2009 Virus within 48 Hours. *Emerging Infectious Diseases* Vol. 16, No. 10, October 2010: 1633-1636 <https://wwwnc.cdc.gov/eid/article/16/10/pdfs/10-0688.pdf>
39. Calatayud L, Lackenby A, Reynolds A, et al. (2011) Oseltamivir - resistant pandemic (H1N1) 2009 virus infection in England and Scotland, 2009-2010. *Emerging Infectious Diseases*, vol 17(10); 1807-1815 [http://wwwnc.cdc.gov/eid/article/17/10/11-0117\\_article](http://wwwnc.cdc.gov/eid/article/17/10/11-0117_article)
40. Myles PR, Semple MG, Lim WS, Openshaw PJM, Gadd EM, Read RC, et al (2012). Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009-2010 in the UK. *Thorax*. 2012 Aug 1;67(8):709–17  
<http://thorax.bmj.com/content/67/8/709.full.pdf+html>
41. Creanaga AA, Johnson TF, Graitcer FC, et.al. (2010). Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. *Obstetrics and Gynaecology*. April 2010- volume 115 – issue 4, pp 717-726.  
<http://journals.lww.com/greenjournal/pages/articleviewer.aspx?year=2010&issue=04000&article=00008&type=abstract>
42. Dabrera G, Zhao H, Andrews N, et.al. (2014). Rapid Communications. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England 2013/14. *Euro. Surveill.*2014;19(45), article 1.  
<http://www.eurosurveillance.org/images/dynamic/EE/V19N45/art20959.pdf>
43. South East Asia Infectious Disease Clinical Research Network (2013). Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. *BMJ*.2013;346,f3039.  
<http://www.bmj.com/content/346/bmj.f3039>
44. Farrukee R, Mosse J, Hurt AC (2013). Review of the clinical effectiveness of the neuraminidase inhibitors against influenza B viruses *Expert Rev Anti Infect Ther*. 2013 Nov;11(11):1135-45 <https://www.ncbi.nlm.nih.gov/pubmed/24093683>
45. Dixit R, Khandaker G, Hay P et.al. (2015). A randomized study of standard versus double dose oseltamivir for treating influenza in the community. *Antivir Ther*. 2015;20(7):689-98.  
<https://www.ncbi.nlm.nih.gov/pubmed/24912485>